

## Psychopharmacology of fluoride: a review

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Although the blood-brain barrier is relatively impermeable to fluoride, it does not pose an absolute barrier and fluoride has the ability to enter the brain. The literature was examined to assess the quality of the evidence for cerebral impairment occurring due to exposure to fluoride from therapeutic or environmental sources. Several surveys of persons chronically exposed to industrial fluoride pollution reported symptoms related to impaired central nervous system functioning with impaired cognition and memory. Examination of individual case reports showed the evidence for aetiological relationships between symptoms and fluoride exposure to be of variable quality. The evidence was seen as being suggestive of a relationship rather than being definitive. The difficulties with concentration and memory described in relation to exposure to fluoride did not occur in isolation but were accompanied by other symptoms of which general malaise and fatigue were central. Possible mechanisms whereby fluoride could affect brain function include influencing calcium currents, altering enzyme configuration by forming strong hydrogen bonds with amide groups, inhibiting cortical adenylyl cyclase activity and increasing phosphoinositide hydrolysis.

**Keywords:** Case reports – Chronic toxicity – Cognition – Cognitive impairment – Concentration – Fluoride – Memory – Psychopharmacology

### INTRODUCTION

Although not used as a psychopharmacologic agent, fluoride from therapeutic or environmental sources is able to enter the brain and thus has the potential to affect cerebral brain function. Yu-huan and Si-shung (1988) noted that fluoride metabolism in the central nervous system had not been thoroughly and systematically studied. They postulated however that fluorine might damage the nervous system directly. This followed seeing patients with high body fluoride levels with nervous system symptoms which improved after they were removed from the higher level of fluoride exposure with a consequent decrease in body fluoride levels. As a recent review of chronic fluorine poisoning in humans (Anand and Roberts, 1990) did not consider the psychopharmacology, a further examination of this area appeared to be appropriate.

### ABSORPTION AND ENTRY OF FLUORIDE INTO THE BRAIN

Whitford (1990) reported that in the absence of high concentrations of divalent and trivalent cations, about 80% of ingested fluoride was absorbed from the gastrointestinal tract. Absorption from the stomach was enhanced by a lower pH suggesting hydrofluoric acid (HF) rather than ionic fluoride was the permeating moiety. Fluoride is not bound by plasma proteins and it is considered that interstitial fluid and plasma fluoride concentrations are

virtually identical. In studies of the soft tissue distribution of fluoride, plasma fluoride levels are used as the reference extracellular concentrations. Plasma fluoride levels increase in proportion to the chronic level of fluoride intake rather than being homeostatically controlled as was once believed. Plasma levels can be used as an index of previous exposure to the ion. HF rather than ionic fluoride is considered to be in diffusion equilibrium across cell membranes. Yu-huan and Si-shung (1988) found that in normal individuals fluoride was in dynamic equilibrium between the blood and cerebrospinal fluid (CSF) with the CSF fluoride being similar to or slightly lower than that in blood. Whitford *et al.* (1979) found a low brain tissue to plasma fluoride ratio of 0.08 1 h after the intravenous injection of fluoride in rats and considered that, at least in the short term, the blood-brain barrier was relatively impermeable to fluoride. Geeraerts *et al.* (1986) similarly found a relative impermeability of the rat blood-brain barrier to fluoride, but noted that the barrier was unable to exclude the fluoride ion from entering nerve tissue. They found that the maximum concentration was reached 2 h after oral ingestion. After 3 h the brain tissue to plasma ratios had a range of 0.05-0.07. In humans a mean brain fluoride level of 1.8 ppm (range 0.2-6.1) has been found in persons exposed to air pollution by fluoride, with the mean for those not so exposed being 1.5 (0.4-3.6) (Call *et al.*, 1965).

## ACUTE TOXICITY

The "probably toxic dose", i.e. the minimum dose that could cause toxic signs and symptoms including death and that should trigger immediate therapeutic intervention and hospitalization, is about 5 mg/kg for fluoride (Whitford, 1990). The affinity of fluoride for calcium may lead to hypocalcaemia manifested by tetany, seizures, depression of the central nervous system and impairment of blood coagulation (Baltazar, 1980). Other cations such as zinc, manganese and magnesium may be rendered unavailable resulting in the inhibition of enzyme systems dependent on these trace metals. Interference by fluoride in the potassium fluxes between red blood cells and serum may lead to hyperkalaemia and a lethal ventricular arrhythmia.

## CHRONIC TOXICITY

Skeletal and dental fluorosis are established manifestations of chronic fluoride toxicity (Singh *et al.*, 1963) but a syndrome of cerebral impairment due to fluoride has not been established to the stage of warranting recognition in standard texts on organic psychiatry (e.g. Lishman, 1987). Roholm (1937), in a study of 68 cryolite workers 84% of whom had skeletal fluorosis, found that 22% had symptoms classified as being of a nervous character, involving tiredness, sleepiness, indisposition, headache and giddiness. Geall and Beilin (1964) described optic neuritis developing in association with the therapeutic use of sodium fluoride. Grimbergen (1974) found by double-blind testing that some individuals developed migraine-like headaches, visual disturbances and depression with a daily intake of 1 mg fluoride. Czerwinski and Lankosz (1977) studied 60 aluminium smelter workers, 97% of whom had skeletal fluorosis, and found 23% to have psychiatric disturbances with depression, mental sluggishness and memory disturbances. Waldbott (1979) studied 23 persons residing within 3 miles of an enamel factory which emitted excessive amounts of airborne hydrogen fluoride. Environmental contamination with fluoride was confirmed by finding excessive levels in vegetation and a domestic animal. A chronological relationship was present between the onset of illness and the commencement of the pollution. Those residing further away from the factory were less affected and had lower urinary fluoride levels. Generalized progressive fatigue was the outstanding feature and was associated with a distinct decline in mental acuity, increased forgetfulness, inability to coordinate thoughts and a reduced ability to write. Neurological symptoms were described in 22 cases involving paraesthesias (15), cephalgia (14), vertigo (7), impaired vision (6) and scotomata (7).

Evidence to support an aetiological relationship between exposure to fluoride and symptoms indicating

central nervous system dysfunction may also come from the study of individuals. The evidence is stronger when an association is found between the presence of symptoms and exposure to fluoride administered in a double-blind manner. Waldbott (1955, 1956, 1962, 1979, 1980, 1983), Waldbott and Lee (1978) and Waldbott *et al.* (1978) have described 11 cases where psychiatric symptoms such as lethargy, memory impairment and difficulties with concentration and thinking came on after exposure to fluoride. This usually occurred with fluoridated drinking water but in three cases involved industrial exposure. The temporal relationship of the symptoms to fluoride was supported by double-blind testing in two individuals, single-blind testing in four, and high environmental fluoride levels in three cases. Two of these persons also had high individual fluoride levels. Similarly Petraborg (1974) described a 36-year-old man who became unwell shortly after his water supply was fluoridated. His symptoms settled with using non-fluoridated water and returned with using fluoridated water. No challenge tests were given. The 12 cases reported by Waldbott, Waldbott and Lee, Waldbott *et al.* and Petraborg are summarized in Table I.

## DISCUSSION

The difficulties with concentration and memory described in relation to exposure to fluoride did not occur in isolation but were accompanied by other symptoms of which general malaise and fatigue were central. Other symptoms included those involving joints, the gastrointestinal system, the urinary tract, peripheral nerves and muscles. The relatively small number of reports of cases and the varying degrees of scientific rigour present in demonstrating a relationship between exposure to fluoride and cerebral impairment support the view that there is suggestive rather than definitive evidence that chronic toxicity affecting cerebral functioning can follow exposure to fluoride.

A number of possible mechanisms exist whereby fluoride could affect cerebral function. In view of the frequency of the symptom of amnesia it is of interest that intracellular fluoride has been found to alter the time course of calcium currents from hippocampal neurones in guinea-pigs (Kay *et al.*, 1986). However although Chan *et al.* (1983) found, of 30 elements studied, that fluorine showed the highest regional differences in the brain in rats, the highest levels occurred in the midbrain, pons and medulla rather than the hippocampus. Emsley *et al.* (1981) noted that the amide-fluoride hydrogen bond was the second strongest hydrogen bond known and that it seemed certain that the fluoride ion was able to compete successfully for the N-H bond in amide systems such as occur in proteins. This was seen as an explanation of how the fluoride ion could disrupt key sites in biological systems. Edwards *et al.* (1984) found that fluoride binding induced significant perturbations in

TABLE I. Case reports

| References                                             | Patient and age      | F source                              | Clinical features                                                                   | Evidence                                                               |
|--------------------------------------------------------|----------------------|---------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Waldbott (1955, 1980)<br>Waldbott <i>et al.</i> (1978) | Mrs MJ,<br>35 years  | Water                                 | Weakness, drowsiness,<br>impaired concentration,<br>impaired memory                 | Temporal association,<br>single-blind testing                          |
| Waldbott (1956)<br>Waldbott <i>et al.</i> (1978)       | Mrs HM,<br>49 years  | Water                                 | Weakness,<br>impaired thinking                                                      | Temporal association                                                   |
| Waldbott (1956)                                        | Mrs CAT,<br>53 years | Water                                 | Weakness,<br>impaired concentration,<br>impaired memory                             | Temporal association                                                   |
| Waldbott (1962, 1980)                                  | Mrs WEA,<br>62 years | Water, toothpaste,<br>trifluoperazine | Lethargy,<br>cerebral lassitude                                                     | Temporal association,<br>single-blind testing,<br>double-blind testing |
| Waldbott (1962)                                        | Mrs ES,<br>57 years  | Water                                 | Lethargy,<br>impaired memory                                                        | Temporal association,<br>raised urine F,<br>single-blind testing       |
| Waldbott (1962)                                        | Mr FLP,<br>61 years  | Water                                 | Lethargy,<br>impaired concentration,<br>impaired memory                             | Temporal association,<br>single-blind testing                          |
| Petraborg (1974)                                       | Mr FT,<br>36 years   | Water                                 | Lethargy, tension,<br>depression                                                    | Temporal association                                                   |
| Waldbott <i>et al.</i> (1978)<br>Waldbott (1980)       | Miss CD,<br>13 years | Water                                 | Reduced mental alertness                                                            | Temporal association,<br>double-blind testing                          |
| Waldbott <i>et al.</i> (1978)                          | Mrs MMc,<br>54 years | Air,<br>Al smelter                    | Weakness,<br>mental confusion,<br>impaired memory                                   | Temporal association,<br>raised environmental F                        |
| Waldbott <i>et al.</i> (1978)                          | Miss CC,<br>24 years | Water                                 | Lethargy,<br>impaired concentration,<br>impaired memory                             | Temporal association                                                   |
| Waldbott and Lee (1978)<br>Waldbott (1983)             | Mr KAM,<br>57 years  | Air,<br>oil alkylation unit           | Weakness,<br>decreased intellectual<br>power,<br>impaired spelling and<br>writing   | Temporal association,<br>raised bone F,<br>raised environmental F      |
| Waldbott (1983)                                        | Mr WJ,<br>50 years   | Air,<br>water plant                   | Lethargy,<br>decreased mental acuity,<br>impaired concentration,<br>impaired memory | Temporal association,<br>raised environmental F                        |

the enzyme structure of cytochrome *c* peroxidase. An active-site arginine residue was considered to move in order to optimize hydrogen-bonded interactions with the fluorine atom thus altering the shape of the active site and the enzyme's activity. In reviewing the subcellular effects of fluoride, Elsair and Khelfat (1988) noted that effects could occur on protein synthesis, the membrane sodium pump, glycolysis, Krebs cycle and oxygen consumption. Jope (1988) found that sodium fluoride stimulated the hydrolysis of phosphoinositides in rat cortical slices. It was considered that this occurred through the formation of aluminium fluoride which activated a G protein which served as a transducer between receptors and

phospholipase C. Phospholipase C, in turn, catalysed the hydrolysis of phosphoinositides to produce two second messengers, inositol triphosphate and diacylglycerol. Aluminium fluoride may also inhibit cortical adenylyl cyclase activity resulting in lower cyclic AMP levels similar to those found in Alzheimer's disease (Cowburn *et al.*, 1992).

## CONCLUSION

There would appear to be some evidence that chronic exposure to fluoride may be associated with cerebral impairment affecting particularly concentration and

memory in some individuals. These symptoms are reminiscent of those seen in the chronic fatigue syndrome. At present the evidence is suggestive rather than definitive. A number of possible mechanisms exist whereby such effects could be mediated. This relationship between fluoride and psychiatric symptomatology warrants further investigation.

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(Received 3 October 1993; accepted 15 October 1993)